

Chapter 2

Built to Last?

Scientists' Views on the Definition, Prediction, Prevention, and Manipulation of Aging

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2.1 Introduction

As time goes by, individuals are deprived of many of the strengths, assets, and affluences they have edified earlier in life. Somewhat tragically, the loss that comes with age is not always graceful and may bereave human beings from some of their most intimate capacities, among which comprehension, appetite, sensitiveness, swiftness, and elegance. Such loss is likely to affect personal identity, independence, social integration, and wellbeing in many elderly individuals. Moreover, dealing with loss will often require a significant share of material and human resources. Whether we like it or not, *life is a losing game*.

Throughout history, the phenomenon of aging has been described and depicted in many ways. There are for example intriguing images of the ages of man, including the three ages of man painted by masters as Giorgione and Titian, or the seven ages of man in the famous monologue *All the world's a stage*. This part of Shakespeare's comedy *As you like it* portrays aging consistently with a commonsensical understanding of the life course, in which growth and decline are observed as a an obvious and natural process, an inescapable part of the human condition. Shakespeare's observation of the final life stage is not particularly flattering: '*Last scene of all, that ends this strange eventful history, is second childishness and mere oblivion, sans teeth, sans eyes, sans taste, sans everything*'. Luckily, it would be all too cynical to still represent old age as mere and inelegant loss, now that old age may present itself rather as a second youth than a second childishness. And also historically, negative depictions of aging have known their counterpart in images of longevity, rejuvenation, and immortality: Methuselah, the fountain of youth, and the elixir of life are just a few illustrations.

The historical accounts of aging, mortality, longevity, rejuvenation, and immortality have recently been challenged by a spectacular demographic evolution and new

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scientific insights in the process of aging. Against this background, images of senescence and old age are being redrafted in science and society, and the very process of aging—rather than age-related problems—has increasingly attracted scientific, ethical, and social interest.

In this chapter, it is explored how scientists define and approach aging in different fields of scientific enquiry. *What problems do they define? Which images of aging do they endorse? What are the objectives of their research? And what research outcomes do they envision?* Based on interviews with 11 leading scientists in different fields of biomedical enquiry, the background, objectives, drivers, results, progress, and way forward of research in the field of aging are explored.

Regardless the considerable variety in disciplines, research areas, and personalities, the views and opinions that were expressed during the interviews are surprisingly complementary. Therefore, it was possible to merge the information that was gathered in the interviews in a considerably coherent discourse.

The information in this chapter is mainly based on the information provided during the interviews. Although at many instances, scientists referred to published data (in general or to specific papers), these data were not explicitly or systematically taken into account in this chapter.

2.2 Aging Revisited

Life expectancy has increased spectacularly over the past two centuries: In entire populations, human beings live about twice as long as their ancestors did a few centuries ago. Over the past 160 years, life expectancy has increase with approximately 6 h for each day that went by (Oeppen and Vaupel 2002). *What factors can explain for this rather sudden increase in life expectancy? What human traits enable us to live longer than our ancestors did? Are there boundaries to further increases in life expectancy? And why does the increase in life length come with a downside?*

To answer these questions, we need to explore the main factors that are constitutive for the way in which we age, and the length of the lifespan we live: Genomics, environment, and lifestyle.

2.2.1 Genomics

Aging often comes with disease, and many diseases come with age. By consequence, it is relatively easy to designate a number of diseases and conditions as ‘age related’. Such designation, however, can rather be an observation than a true understanding of the relationship between aging and disease. In order to explain *why* aging induces an increased mortality rather than *that* aging induces such increased mortality, insight in the biology of aging is required.

Over the past decades, new technologies have created very important opportunities to study the biology of aging, and such technologies continue to develop rapidly.

Genetic sequencing is exemplary in this respect: Since the discovery of the structure of DNA by Watson and Crick in 1953 and the first sequencing of an entire human genome in 2004, techniques for genetic sequencing have become much faster and cheaper. By consequence, the amount of genetic data that is generated is increasing exponentially, as scientists move from studying single genes, to exome sequencing (the mapping of approximately 30.000.000 base pairs), and currently towards full genome sequencing (*i.e.* 200-fold more). This has transformed the challenge of generating data into the challenge of processing and analysing data.

The analysis of genetic data can result in the discovery of defects in a single gene (e.g. a defect resulting in the generation of an inactive protein encoded by the gene) or in associations between genes and human traits, conditions, and diseases. Such associations are identified in large population studies, covering thousands of human subjects. For example, a study of genetic variance in height involved genomic data from 180.000 individuals.

Now that scientists are capable of gaining insights at the molecular level and sequencing the entire genome, what does this reveal about the process of aging? First, aging occurs in many organisms and species. Particularly organisms that reproduce sexually are vulnerable to aging, because there appears to be a trade-off between reproductive success and longevity in these organisms. From the viewpoint of evolutionary biology, selection in function of species survival lacks a rationale to promote population-wide longevity beyond a lifespan that is relevant for successful reproduction. This may explain why we experience so many age related problems now that our lifespan clearly exceeds the period that is relevant for conceiving and raising children (about 35–45 years, corresponding well with the life expectancy up to 1800). This may also explain that healthy aging appears to be a privilege of the lucky few to date. Second, if aging was not selected for, there is no purpose in aging and longevity from a biological point of view. Rather than being a functional biological process, aging seems to be a side effect of increased longevity due to man-made environmental changes. Among the interviewed scientists, there was even discussion whether aging is a biological process at all. Regardless the definition of aging as a biological process or not, there appears to be considerable consensus on what happens when we get older: The body loses part of its capacity to regenerate and to repair defects, and accumulates damage. Loss of regenerative capacity and accumulation of damage render the body more vulnerable to various pathologies, which may induce multimorbidity in elderly individuals and increase the likelihood of mortality. And also in absence of disease, the loss of regenerative capacity and accumulation of damage will affect the composition and functioning of the body and induce frailty. Third, genetics in itself cannot account for the changes in the length of our lives and the way in which we age. Given the fact that two centuries is a very short timespan in terms of natural selection, the spectacular increase in life expectancy in many societies cannot be explained by significant changes in the genome. Rather, such a sudden increase in longevity suggests the importance of other factors: The environment and personal lifestyle. This has implications for what genetic research can reveal. Given the millions of differences between the genomes of individual human beings, studies of the genome of long living subjects (for example, Mrs Andel, a

Dutch woman who was for some time the oldest person alive and disposed her body to science) are not replicable and will not enable scientists to unravel the ‘secret’ of longevity. Even if it is possible to associate genetic variance to longevity, such associations cannot give a clear indication on how long an individual will live, or whether someone will age in relatively good health or not. In addition, studies of the genome in twins revealed that, in general, the heritability of longevity is about 25 %, clearly suggesting that the length of our lives is influenced strongly by other factors than our genes. Fourth, aging is very heterogeneous. Individual beings grow and age at a different pace and in a different way. Also within one and the same individual, different tissues and organs appear to age at a different pace and in a different way. This renders it hard to define at what age aging sets in. As has already been pointed out, the personal genome only partly accounts for differences between aging individuals, since the heritability of longevity is rather limited. Some individuals born in long-living families, however, appear to have a genetic advantage for living long and in relatively good health. In these families, the heritability of longevity is higher than in the population at large: about 40 to 45 %. Fifth, aging has a high plasticity and is therefore open to manipulation. On the one hand, aging can be manipulated by changes in the environment and lifestyle. Caloric restriction is a well-known example in this respect: When the caloric intake of an organism (for example yeast, worms, mice, and monkeys) is restricted with 25–30 % in comparison to an organism that is fed ad libitum, longevity increases significantly. In addition, research in epigenetics demonstrates that environmental and lifestyle factors strongly influence the phenotypic expression of genes, from the very start of life onwards. For example, a large study of persons who suffered from prenatal malnutrition during gestation (born in Amsterdam between 1943 and 1947, in wartime conditions with food rations from only 400–800 kCal/day) revealed an increased incidence of diabetes, cardiovascular disease, hypercholesterolemia, obesity (in women), and many other health problems in this population.¹ This shows a considerable plasticity of aging and implies that, even if we are all unequal at the start, healthy aging needs not to be a privilege of the lucky few.

2.2.2 *Environment*

It has already been suggested that environmental changes are particularly relevant to the increase in life expectancy that occurred over the last two centuries. What changes in our environment have paved the way for humans to live so many years longer?

First, better hygiene has contributed to the significant reduction of the risk of infections and inflammations, and thereby eliminated a large number of preventable deaths. At the public level, important efforts have been made to provide people with clean (chlorinated) water and clean living environments (e.g. waste collection). At

¹ See: www.hongerwinter.nl

the personal level, personal hygiene has improved, for example due to the broad availability of soap and clean water. Second, the availability and quality of food have strongly improved. New techniques to produce, pack, and conserve food have rendered people less dependent on factors that are out of our control, such as favourable weather conditions. Apart from the availability and quality of food, also the quality of our diet has improved, by moving towards a more balanced diet in which all essential nutrients (e.g. proteins, fats, fibres, vitamins) are adequately represented. Third, our living conditions have been strongly improved by building better infrastructure in terms of for example housing, labour, transport, social contact, communication, and leisure. Fourth, biomedicine has been very successful in the timely diagnosis, prevention, and treatment of many conditions and diseases. Vaccines, antibiotics and other drugs, operative interventions, imaging techniques etc. have contributed significantly to better health and longer lives.

Together, these four factors have changed the way in which we age, not only as individuals, but also as populations. Indeed, the increase in longevity that has taken place over the past two centuries can be observed in entire populations. Once again this illustrates that aging is certainly not a privilege of the lucky few. A classical, almost iconic example of longevity in entire populations is Japan, the country that hosts the highest rate of long living people worldwide. Such an example clearly shows that man-made interventions in the environment can induce large and fast increases in longevity in entire populations. The short time span in which the recent increase in life expectancy took place, precluded human organisms to adapt to these changes timely through selection via reproduction. By consequence, the body outlives the lifespan it was selected for and functions in an environment it was not selected for. This explains why longevity has not just increased, but increased longevity has caused numerous health related problems.

2.2.3 *Lifestyle*

Changing environments can work in favour of longer lives. But this is not always the case: Changing environments can also transform assets into perils. For example: If selection has rewarded the capacity to survive periods of famine, organisms become more vulnerable to obesity. And if selection has adapted organisms to a diet of food that is extracted from the near environment, switching to a diet of ready to consume food in which sugar is overrepresented renders organisms more vulnerable to diabetes. By consequence, there is a new killer in town: *lifestyle disease*.

It has become increasingly clear that in an aging and society where living conditions are largely man-made, one must be vigilant of man-made health problems, including lifestyle diseases. The situation in Okinawa, the Japanese province with the highest rate of centenarians, clearly illustrates this situation. While the centenarians in Okinawa can be regarded as a paradigmatic example of increased longevity, a considerable decrease in life expectancy can be observed in their grandchildren due to lifestyle changes. Another notorious example in this respect is Glasgow, where

the local lifestyle has generated a longevity gap of about 14 years with Kensington, London.

While Okinawa and Glasgow illustrate that differences in lifestyle may generate differences in life expectancy of entire communities, the same is also true for individuals. Smoking, unhealthy diet, inactivity, and stress are major examples of lifestyle factors that negatively affect health and life expectancy of individuals. Also social factors, such as the educational level, creates longevity gaps of up to 7 years.

The importance of lifestyle can hardly be overestimated. One of the interviewees in this study emphasized that in absence of an appropriate lifestyle, medical interventions are not likely to be effective. It is thus not an option to search or wait for a magic bullet that allows us to endorse an unhealthy lifestyle and address all health problems with medical quick-fix interventions. The definition of a healthy lifestyle by the interviewed scientists does not reveal unexpected recommendations: Sufficient fruit and vegetables, no smoking, sufficient physical activity, and moderate wine consumption (2 glasses/day) (Khaw et al. 2008).

Together, genomics, environmental factors, and lifestyle suggest that aging is a highly complex phenomenon. Despite this complexity, there seems to be a substantial potential to explain, predict, prevent, and/or treat various problems that come with age. What actions, then, do scientists undertake to understand, predict, and manipulate the way in which young people become old, and old people experience the perils of old age.

2.3 Work in Progress

For many reasons, research in the field of aging is booming. On the one hand, people continue to live longer, many long-living individuals suffer from multiple (chronic) diseases, and societies at large are challenged to take care of an ever-growing number of frail elderly. Therefore, the urgency to deal with the health problems in the elderly is high, and research in various aspects of senescence and aging is most relevant. On the other hand, aging provides scientists in various field of enquiry with a solid framework to formulate research questions, interconnect data and disciplinary approaches, and interpret research outcomes. Regardless whether scientists focus on the study of disease, the genome, genetic expression, or social determinants of health and well-being, framing research in the context of aging (1) provides a relevant background against which research questions can be formulated and (2) integrates specific research in a broader, multidisciplinary, and socially highly relevant framework. Such framework sheds a new light on research findings: If we try to understand the complex process of aging in which genomics, environment, and lifestyle all play a key role, an incredibly large amount of research findings will be deemed relevant, even when such findings currently lack clear significance on their own, or lack potential to contribute to the development of clinical applications or patient care.

The fact that scientists enquire aging from multiple perspectives and disciplinary approaches, renders research in this domain very heterogeneous in its objectives, methods, and outcomes. At the same time—at least for what concerns the scientists who were interviewed in this study—these heterogeneous objectives, methods, and outcomes are rather complementary than contradictory.

According to the interviewed scientists, it is unlikely that aging as such will be eliminated. Even with an excellent maintenance of the body, a minimization of environmental challenges, and a maximisation of adequate bodily response to environmental challenges, aging will still be present in man. Like with a car, maintenance may help to keep it going much longer in a relatively good condition, but inevitably, it is bound to get exhausted at a certain point in time. In the end, we are not *built to last*.

If elimination is not the focus of research in the field of aging, what is? In their research, the interviewed scientists focus on (1) the biology of aging, (2) age-related diseases, (3) healthy aging, and (4) adequate care. These four domains are certainly not distinct fields of enquiry. However, for reasons of comprehensiveness and somewhat reductionist, they will be explored as four focal areas in this chapter.

2.3.1 *Biology*

Scientists may focus their endeavours on the biology of aging. The main aim of this type of research is to gain insight in the complex biological background of aging. How can aging be understood from the viewpoint of evolutionary biology? What is the genetic basis of senescence and longevity? What causes the degeneration of the body, resulting in loss of functionality and increased frailty? What is the role of specific cells, such as stem cells? What is the role of specific mechanisms, such as DNA repair? To gain an answer to this type of questions, genetic data are of key importance. It has already been pointed out that over the last decades, the sequencing of genes en entire genomes has become cheaper and faster. This enables to compare genetic data of thousands of individuals in large association studies, with the objective of revealing what genes are involved in aging and age related diseases. What results then, do such association studies generate? Most of all, association studies show that most age related conditions are complex, and involve many genes. For example, association studies identified about 95 genes related to hypercholesterolemia, and 80 genes related to osteoporosis. Linking genetic variance to particular age-related diseases is one thing, understanding the specific role of all the genes involved, however, is quite another. While a lot is known about some parts of the genome, other areas—so called gene deserts—have no known functional importance. This clearly impairs the explanatory powers of findings that associate genetic variance with particular age related diseases or conditions.

The fact that so many genes are involved in different kinds of biological processes has implications for the predictive power of genetic analyses. Can genetic markers help to predict health risks and/or diagnose diseases (already before the onset of

pathologies) in a reliable way? For various diseases, including diabetes, cancer, and cardiovascular diseases, genetic markers have been identified. The predictive value of such markers however, seems questionable. For example, a study measuring successful markers for various diseases in a population of members from long-living families, indicated that the markers for these diseases were equally well represented in long living families than as in other populations. This clearly suggests that with the worst set of genetic markers, people may still grow very, very old.

The fact that many genes are involved in different kinds of biological processes also has firm implications for the manipulation of these processes. Given the high number of genes involved, and the (indirect) interaction of genes in genetic processes, manipulation is very complex. Many genetic processes have alternative pathways, and therefore tweaking particular genes will not suffice to do the trick. Rather, some sort of systems approach is required to get a grip on the process itself, and not just the functioning of a particular gene in this process.

Apart from the study of the human genome and the relationship between genetic variance and diseases and conditions, also animal research is very important. Animals have a shorter lifespan and can be nurtured in controlled conditions from conception to death, selected on genetic traits, bred with identical genomes, involved in experiments that would never be allowed in humans (for example experiments with stem cells or DNA repair), and sacrificed for the sake of science. Obviously, this opens up many research opportunities.

To date, genetic research in animals and humans has generated numerous findings that provide new insight in the genetic background of aging. However, for the bulk of these findings, translation into the clinical applications is not likely to take place in the near future. This seems not to be of major concern to the interviewed scientists. Rather than developing high-tech interventions in the genome to counter age related health problems (or to extend life further), their research seems to focus on a better understanding of genetic mechanisms in service of prevention, diagnosis, prediction, and the optimization of available therapies. As one researcher stated: “One could say: If it is my objective to help people age healthily, then I can stop doing my research in molecular biology. Because there is one thing that certainly will enable many more people to age healthily, and that is getting them—from middle age on—to have sufficient physical activity and a healthy diet. In fact, we already know that.”

2.3.2 Disease

Regardless whether aging is considered a disease or not, the incidence of many diseases increases with age. By consequence, morbidity is higher in older subjects in comparison to their younger counterparts. *What renders elderly more vulnerable to disease? How can the risk to age-related diseases be reduced? When should prevention and treatment start? How can the onset of age-related diseases be postponed? How can imminent health threats be averted? How can morbidity be compressed further? How should multimorbidity in elderly be managed in healthcare? And what*

are the standards of good health in the elderly, when one recognizes that a certain degree of degeneration and/or ill-health is inevitable? All these questions trigger research in the field of age-related diseases.

How do researchers envision the future impact and approach of age related diseases? Although life expectancy continues to increase, scientists pursue to decrease the timespan in which elderly suffer from various ailments. So research aims to contribute to a further rectangularization of the survival curve (Fries 1980) due to a further compression of morbidity. Several complementary and interrelated strategies are developed in this respect: (1) reducing of the risk to disease, (2) postponing the onset and/or slowing down the progress of diseases, and (3) reducing mortality from age-related diseases such as heart disease, cancer, and stroke.

First, whether an individual will start to suffer from age-related diseases is not just a matter of fate. Research at the intersection of genomics, environment, and lifestyle, enables scientists to search for different types of interventions that will reduce the risk to diseases. Here, it is all about a proactive and personalized approach to health and disease. Instead of awaiting pathologies and health complaints before entering the clinic, predictive tests would enable to tackle disease before pathologies develop and morbidity increases. To optimize primary, secondary, and tertiary prevention, it is enquired how health can be assessed and addressed in a timely fashion. Also a personalized approach is important in this respect: Since phenotype plasticity renders it possible to regulate the expression of genes to a certain extent (e.g. through environmental or lifestyle interventions), a personalized approach of health could aim at tweaking the genome in such a way that health problems are averted and risks are reduced.

Second, also when an individual will start to suffer from age-related diseases is not written in stone. Given the considerable plasticity of aging, age-related pathologies can be postponed and/or slowed down. For example, a healthy lifestyle will contribute to the good condition of tissues from early on in life, which is advantageous throughout the entire degeneration process. Those who are ahead at the start can cope with a larger degenerative losses before developing diseases. And those who invest in maintenance of their body can slow down the pace of the aging process. Or, for example applied to sarcopenia, individuals who developed more skeletal muscle mass at the peak of development, are able to cope with more loss of muscle mass before developing actual sarcopenia.

Third, when focusing on disease, also the main causes of mortality are targeted. New technologies can help to study how disease can be treated more effectively in aged bodies. For example, mouse skin cells have been reprogrammed to heart cells that are beating in vitro (Efe et al. 2011). Such cell cultures offer new opportunities to test the efficacy of drugs.

Combatting the main causes of mortality can also come with a downside. By addressing preventable causes of death, aging, senescence, and mortality will not be eliminated altogether. By consequence, the successful approach of one disease will thus not just discharge us from ill health, but also pave the way for other health problems. In other words, the successful approach of one disease may thus come at the cost of getting another. For example, now that some causes of preventable death

are addressed adequately, dementia is on the increase. By consequence, rather than avoiding death, we may be choosing to die another day. Such choice may come at a high cost, since it may destabilize the overall frailty that enables human beings to degenerate slowly until they are completely worn out. By consequence, the end of life may become ill, rather than frail.

2.3.3 *Health*

Although one needs not to be healthy to be happy and good health, for its part, is no guarantee for happiness at all, health is highly valued. No wonder then that scientists search for strategies to age healthily.

How do scientists define a good health in elderly life? As has already been pointed out, in the views of the interviewed scientists, aging healthy is certainly not synonymous to the elimination of health problems in the elderly. Rather, the idea of good health in old age is inspired by models of healthy aging, such as members of long-living families, who live longer than average in a relatively good health.

If 'healthy agers' are the lucky few that can serve as a model for aging in good health, can something be done to enable the population at large to resemble these models? Research points out that this is certainly the case. For example, a the study of partners of members of long-living families, who obviously do not automatically share a similar set of genetic traits that favour healthy aging, can start to resemble their partners in the way in which they age as the outcome of a program of adequate lifestyle interventions, including healthy diet and physical activity. If initially the two partners have a different 'molecular profile' of aging, this profile is open to change, and changes can be measured within weeks, or at least three months from the start of such a program. The challenge ahead here, seems to tweak the genome is such a way that health and longevity are promoted. An overall objective here is to reduce the heterogeneity in the way in which individuals age, and to contribute to narrowing existing longevity gaps.

There is a broad consensus among the interviewed scientists that prevention and appropriate lifestyle is *the* way to gain in health in elderly life. It must be emphasized, however, that this observation needs not to work against basic research. Indeed, the importance of lifestyle does not suggest the priority of research in lifestyle interventions over basic research in any way. For example, if basic research can provide insight in the risks to diseases of individual persons, these findings can be used to support an adequate response to these risks.

What then, is constitutive for a lifestyle that supports longevity and healthy aging?

First, efforts can be made to discharge the human organism from harmful environmental challenges. For example, overloads of sugar, fat, or calories in general in the diet cause metabolic stress. Reduction of caloric intake and a balanced diet (e.g. the Mediterranean diet) will contribute to increased health and longevity. Also the reduction of other environmental challenges, such as smoking and stress is important in this respect. Second, the capacity of human organisms to respond to environmental

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